TRICHLOROETHYLENE
CAS No. 79-01-6
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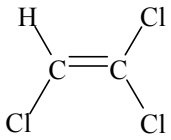

CARCINOGENICITY

Trichloroethylene (TCE) is *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of malignant tumor formation in experimental animals, and convincing relevant information that trichloroethylene acts through mechanisms indicating it would likely cause cancer in humans.

Epidemiological data are limited for evaluating the carcinogenicity of trichloroethylene in humans. Studies have suggested that occupational exposure to TCE causes cancer of the liver and biliary tract, and also non-Hodgkin's lymphoma (IARC V.63, 1995). Another study has indicated that occupational exposure to TCE has been associated with cancer of the kidneys (Henschler et al., 1995a,b; Brüning et al., 1997). Results of three cohort studies consistently indicate an excess relative risk for cancer of the liver and biliary tract, with a total of 23 observed cases, whereas 12.87 were expected (RR = 1.8), and a moderately elevated risk for non-Hodgkin's lymphoma (IARC V.63, 1995). Further, the suggested marginally increased risk for non-Hodgkin's lymphoma in areas with trichloroethylene-contaminated ground water deserves mention (IARC V.63, 1995). For a cohort of cardboard workers exposed almost exclusively to high levels of TCE, the standardized incidence ratio for kidney cancer was 7.97 (95% CI = 2.59-18.59) (Henschler et al., 1995a).

The findings in humans are predated and supported by evidence in experimental animals. Target site concordance for TCE-induced tumors is consistent between humans and rodents. In mice, TCE causes increases in benign and malignant tumors of the liver (NCI 2, 1976; Maltoni et al., 1988; cited by IARC V.63, 1995; NTP 243, 1990), increases in tumors of the lung (Maltoni et al., 1988; cited by IARC V.63, 1995), and lymphomas (Henschler et al., 1980). In rats, TCE induces cancers of the kidney (Maltoni et al., 1988; cited by IARC V.63, 1995; NTP 243, 1990; NTP 273, 1988), interstitial cell tumors of the testis (Maltoni et al., 1988; cited by IARC V.63, 1995; NTP 273, 1988), and possibly leukemias (Maltoni et al., 1988; cited by IARC V.63, 1995).

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

Mechanistically, renal cell carcinomas (RCCs) from workers occupationally exposed to high levels of TCE exhibited somatic mutations of the von Hippel-Landau (VHL) tumor suppressor gene, a gene that has been associated with renal cell carcinomas (Brüning et al., 1997). RCC tissues from all 23 TCE-exposed persons [mainly from Henschler et al. (1995a) cohort] analyzed thus far showed aberrations of the VHL gene, with 30% having aberrations in exon 1, 44% in exon 2, and 26% in exon 3. By comparison to TCE-unexposed RCC patients, VHL mutation frequencies of 33-55% were found in different cohorts, with about 24% affecting exon 2.

There is biological plausibility of the kidney tumors observed and TCE exposures because (1) site and histopathological characteristics of the tumors observed in patients and in experimental animals are identical (Vamvakas et al., 1993); (2) the molecular mechanism of this type of nephrocarcinogenicity has been elucidated (Dekant et al., 1986; cited by IARC V.63, 1995 and Bernauer et al., 1996); (3) the metabolites derived from the likely ultimate electrophilic intermediates of the bioactivation of TCE are identical in humans and in experimental animals (Birner et al., 1993; cited by IARC V.63, 1995 and Clewell et al., 1995); and (4) taking the key urinary metabolites (mercapturic acids) as an indicator of the bioactivation of TCE (Birner et al., 1993; cited by IARC V.63, 1995 and Clewell et al., 1995), humans seem to be more sensitive than rats in developing the primary biochemical lesion leading to the induction of renal cancer.

Rodents exposed to TCE typically exhibit dose-related cytomegaly of the kidneys, the lesion often being more severe in males, with none or few being found in male or female vehicle-control mice or rats. Toxic nephropathy commonly occurs in the solvent-exposed rodents, likewise being more frequent and more severe than seen in controls. In humans, substantially more cases of tubule cell damage were found among renal cell carcinoma patients who had been exposed to high levels of TCE over many years than among RCC patients who had not been exposed to TCE (Henschler et al., 1995a).

Studies of chromosomal aberrations, aneuploidy, and sister chromatid exchanges in peripheral lymphocytes of workers exposed to TCE were considered inconclusive. In rodents, TCE did not induce chromosomal aberrations, dominant lethal mutations, sister chromatid exchange, or unscheduled DNA synthesis, whereas an increase in micronuclei and DNA single-strand breaks/alkaline labile sites was observed. TCE did not induce gene mutations in human cells. In mammalian cells *in vitro*, TCE induced cell transformation, sister chromatid exchange, and gene mutations, but not chromosome aberrations (IARC V.63, 1995).

PROPERTIES

TCE is a colorless liquid with a sweet, chloroform-like odor. Upon combustion TCE produces irritants and toxic gases, which may include hydrogen chloride. In the presence of moisture and light, it decomposes by forming hydrochloric acid (HSDB, 1997).

USE

TCE is used mainly as a degreaser for metal parts. Five main industrial groups use TCE in vapor or cold degreasing operations: furniture and fixtures, fabricated metal products, electrical and electronic equipment, transport equipment, and miscellaneous manufacturing industries (IARC V.63, 1995). TCE can be used as an extraction solvent and a chemical intermediate and as a component in adhesives, lubricants, paints, varnishes, paint strippers, pesticides, and cold metal cleaners (ATSDR, 1995-H008).

PRODUCTION

IARC (V.63, 1995) reported that two companies in the United States produced TCE ca. 1992 with a combined annual capacity of 160,000 tons (145,000 metric tons or Mg). The SRI *Directory of Chemical Producers in the United States* listed only one producer (SRIa, 1996).

EXPOSURE

Air is the primary route of potential environmental exposure to TCE. Most of the TCE emissions into the atmosphere are from vapor degreasing operations. Mean TCE background levels in air range from 0.03 parts per billion (ppb) (0.16 $\mu g/m^3$) in rural areas to 0.46 ppb (2.5 $\mu g/m^3$) for urban and suburban areas. Areas near emission sources have up to 1.2 ppb (6.4 $\mu g/m^3$) TCE in the air (ASTDR, 1995-H008).

The Toxic Chemical Release Inventory for 1995 (TRI95, 1997) contains reports on environmental releases of TCE from 717 U.S. facilities. Of these, 591 reported releases to the atmosphere of more than 2000 lb (0.9072 Mg), with releases ranging from 2000 to > 200,000 lb. The total amount of TCE released in 1995 by the 717 facilities was 25,484,235 lb (11,559 Mg), while the 17 greatest emitters together released 6.1 million lb (2770.4 Mg). The greatest releases were generally from metalworking facilities, with 3 sites each reporting under Standard Industrial Classification (SIC) codes 3317 (steel pipe and tubes) and 3714 (motor vehicle parts and accessories). Other facilities (1 each) reported under SICs 3089 (plastics and plastic products, not elsewhere classified), 3671 (electron tubes), and 3721 (aircraft).

TCE is one of the volatile organic compounds (VOCs) measured in the U.S. EPA's large-scale Total Exposure Assessment Methodology (TEAM) studies (Wallace et al., 1996). In studies in the United States (Maryland, New Jersey, and California) in the 1980s (1981-1987), determination of TCE exposure via personal air monitors carried by 750 persons for two consecutive 12-hour periods revealed TCE median personal air concentrations of 0.3 to 3.0 $\mu g/m^3$. Breath samples taken in the evenings after several hours at home from 50 to 350 persons in two New Jersey cities in 1981-1983 and 75 persons in two California towns in 1984 had 0.1 to 0.9 μg TCE/m^3 (median personal air concentrations of 1.7-3.0 $\mu g/m^3$). However, in 1984 and 1987, TCE was not detected in the breath of 140 persons in Los Angeles, CA (personal air levels were 0.3-1.2 $\mu g/m^3$), nor in 1987 in 75 persons in Baltimore, MD (personal air levels were 1.1 μg TCE/m^3).

Industrial discharges of wastewater streams are the primary release of TCE into aquatic systems. TRI95 (1997) includes data from 28 facilities that had each released more than 10 lb (4.5 kg) TCE to water in 1995. Five facilities each released 250 to 280 lb (114 to 127 kg). The total release of TCE to water was 1477 lb (0.670 Mg). Four of the five facilities were metalworking plants; one was a plant that produced TCE as a by-product and for onsite use and processing. TCE background levels in large bodies of water range from 0.001 to 0.007 ppb ($\mu g/L$), while values reported for rainwater and snow are 0.0008 to 0.039 ppb ($\mu g/L$) TCE (Gist and Burg, 1995). In the U.S. EPA's Contract Laboratory Program Statistical Database, TCE was found in approximately 3% of surface water samples and 19% of groundwater samples at geometric mean surface water concentration of 40.2 ppb (individual sample values ranged from 0.0001 to 120 ppb) and geometric mean ground water concentration of 27.3 ppb (individual sample values ranged from <0.1 to ≤27300 ppb) (USEPA, 1989; cited by IARC V.63, 1995). The total releases of TCE to land and underground injection wells in 1995 were 3577 lb (1.622 Mg) and 550 lb (0.249 Mg), respectively (TRI95, 1997).

TCE is present in typewriter correction fluids, paint removers, strippers, adhesives, spot removers, and rug-cleaning fluids (Gist and Burg, 1995). Former uses of TCE as an extraction solvent for cosmetic and drug products and as a dry cleaning agent have been discontinued (IARC V.63, 1995).

TCE has been found in a variety of foods with the highest levels being found in meats, 12-16 ppb (0.09-0.12 $\mu mol/kg$), and U.S. margarine, 440-3,600 ppb (3.35-27.4 $\mu mol/kg$)

(ATSDR, 1995-H008). TCE had been used as an extraction solvent for natural fats and oils, spices, hops, and caffeine (from coffee), but FDA banned these uses in 1977 (IARC V.63, 1995).

According to the National Institute for Occupational Safety and Health (NIOSH, 1990), 401,373 employees in 23,225 plants in the United States National Occupational Exposure Survey (1981-1983) were potentially exposed to TCE.

REGULATIONS

EPA regulates TCE as a Hazardous Air Pollutant under the Clean Air Act (CAA) 1990 Amendments and as a Volatile Organic Compound (VOC) subject to emission standards under the CAA Section 111 (40 CFR Part 60, 1995) (CHEMLIST, 1997).

Under the Safe Drinking Water Act, the Maximum Contaminant Level (MCL) for community and nontransient, noncommunity water systems is set at 0.005 mg/L (40 CFR Part 141, 1996) (CHEMLIST, 1997). The World Health Organization (WHO, 1993) recommended a provisional guideline value for TCE in drinking water of 0.070 mg/L. Based on a 1985 study by Buben and O'Flaherty, WHO (1993) calculated a total daily intake (TDI) of 0.0238 mg/kg bw by applying an uncertainty factor of 3000 to the study's LOAEL (lowest observable adverse effect level) of 100 mg/kg bw/day when mice were exposed for 5 days/week for 6 weeks. The observed adverse effects were minor effects in relative liver weight. Ten percent of the TDI was allocated to drinking water to derive the provisional guideline value of 70 µg/L.

TCE is regulated under RCRA as a Halogenated Organic Compound (HOC) and under the Land Disposal Restrictions. Under the latter, hazardous wastes that contain total concentrations of HOCs of at least 1000 mg/L (liquids) or 1000 mg/kg (nonliquids) are prohibited from land disposal. Under 40 CFR 268.40 and 268.48, treatment standards are given for wastewater and nonwastewater extract concentrations, or the applicable Technology Code (40 CFR 268.42) is given (CHEMLIST, 1997).

TCE is regulated under Sections 110 and 313 of the Superfund Amendment Reauthorization Act (SARA). Priority data needs established under Section 110 include exposure levels in humans living near hazardous waste sites and other populations and epidemiological studies on health effects, including carcinogenicity. Under EPCRA Section 313 (Community Right-to-Know and the Toxic Chemical Release Inventory [TRI], 40 CFR Part 372 Subpart D, 1992), TCE is one of the 19 substances for which the de minimus for reporting changes from 1.0 percent to 0.1 percent. Under TRI, since 1989, manufacturers of at least 25,000 lb/yr (11,350 kg/yr) and other handlers of at least 10,000 lb/yr (4,540 kg/lb) must report releases of TCE to any environmental medium. Under 40 CFR Part 302 Table 302.4, TCE is on the CERCLA List of Hazardous Substances with an RQ for reporting releases of 100 lb (45.4 kg) or more (CHEMLIST, 1997).

TCE is regulated under the Clean Water Act (CWA) Sections 301, 307, and 311 (40 CFR Part 423, 1996; 40 CFR Parts 116 and 117, 1996). TCE is a priority pollutant in final discharges resulting from steam electric power generation. It is designated a hazardous substance if discharged to navigable waters. The Reportable Quantity (RQ) for notification is 100 lb (45.4 kg) (CHEMLIST, 1997).

FDA regulations govern the presence of TCE in color additives, bottled water, food as extraction solvent residues, and as indirect additives as migrants from adhesives, etc., used in food packaging.

The OSHA Permissible Exposure Limit (PEL) for time-weighted average (TWA) exposure in a 40-hour work week to TCE in workroom air is 100 ppm (537 mg/m^3) with a ceiling value of 200 ppm (1070 mg/m^3) (29 CFR 1910.1000, 1996 [CHEMLIST, 1997]). NIOSH considers TCE to be a potential occupational carcinogen, recommending that exposure be limited to the lowest feasible concentration. NIOSH recommends a REL (Recommended Exposure Level) of 2 ppm (11 mg/m^3) during use of TCE as an anesthetic and a 10-hour TWA of 25 ppm (130 mg/m^3) during all other exposures (Ludwig, 1994). The Threshold Limit Value (TLV®) recommended by ACGIH is 50 ppm (269 mg/m^3); the Short-Term Exposure Limit or Ceiling recommended is 100 ppm (537 mg/m^3). ACGIH (1996) classified TCE as A5 (*Not Suspected to be a Human Carcinogen*). Regulations are summarized in Volume II, Table B-145.